Inhibition of Clinical Benefits of Aspirin on First Myocardial Infarction by Nonsteroidal Antiinflammatory Drugs

To the Editor:

We read with great interest the article by Kurth et al., which suggested that regular use of nonsteroidal antiinflammatory drugs (NSAIDs) inhibits the clinical benefit of aspirin in the primary prevention of myocardial infarction (MI). Several factors might account for this increased risk of MI.

First, we agree that concomitant administration of NSAIDs antagonizes the irreversible platelet inhibition induced by aspirin. Nevertheless, this pharmacological evidence seems difficult to reconcile with the clinical observation of a higher risk of peptic ulcer bleeding in patients receiving aspirin and NSAIDs than in patients receiving aspirin alone. Two other parameters also deserve further consideration in the Kurth et al. study. Regular use of NSAIDs was associated with the highest prevalence of arthritis (6.9% versus 1.8% and 0.8% in the groups using intermittent and no NSAIDs, respectively), which suggests a higher prevalence in this group of active inflammatory rheumatic diseases, including rheumatoid arthritis (RA), the most common systemic autoimmune disease, which affects 600,000 American men. However, active inflammatory rheumatic diseases, such as RA or systemic lupus erythematosus (SLE), are associated with increased cardiovascular morbidity and mortality. In a recent study, women suffering from RA for at least 10 years had a risk of myocardial infarction of 3.10 (95% CI, 1.64 to 3.87). RA and cardiovascular diseases share common pathogenic backgrounds such as the major role of T cells and certain proinflammatory cytokines and increased serum levels of C-reactive protein (CRP). Interestingly, the adjustments for covariates did not include serum CRP, a predictive factor for cardiovascular events, which is often markedly increased in RA patients. Likewise, serum HDL cholesterol, reported to be decreased in patients with active RA, was not taken into account.

Finally, the issue of concomitant medication in the study population was not addressed. Methotrexate provides a substantial survival benefit in RA patients, largely by reducing the cardiovascular mortality. Conversely, the lipid profile could be impaired by frequent use of corticosteroids in patients with RA or SLE.

In conclusion, the differences between the three groups of the Kurth et al. study population might not be restricted to use of NSAIDs, but could also involve the repartition of active inflammatory rheumatic diseases and concomitant medication. These data need to be analyzed in order to fully understand the apparent inhibition by NSAIDs of the beneficial effect of low-dose aspirin in the primary prevention of MI.

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Response

Gottenberg and colleagues raised the question whether arthritis, its treatment, or other related variables confound our observation that regular nonsteroidal anti-inflammatory drug (NSAID) use inhibits the clinical benefit of aspirin on first myocardial infarction (MI). We agree that patients with arthritis are more likely to use NSAIDs regularly and that patients with rheumatoid arthritis have increased risk of MI.

With respect to our study, however, confounding is unlikely because aspirin use was randomized. The sample size was large, and treatment assignment was not associated with NSAID use. Thus, in our randomized sample of 22,071 participants, any potential confounders, including arthritis, its treatment, or other variables such as C-reactive protein, and HDL cholesterol, would almost certainly be equally distributed between the aspirin and placebo groups. We believe that the most plausible interpretation of our data is that regular NSAID use inhibits the clinical benefit of aspirin on first MI.

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